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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



REC'D 04 JAN 2005

WIPO PCT

Applicant's or agent's file reference DES/P33137	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/12181	International filing date (day/month/year) 30.10.2003	Priority date (day/month/year) 01.11.2002
International Patent Classification (IPC) or both national classification and IPC C07C63/331		
Applicant GLAXO GROUP LIMITED		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 7 sheets, including this cover sheet.  
  
☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of    sheets.

- This report contains indications relating to the following items:
  - I    ☒ Basis of the opinion
  - II   ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV   ☐ Lack of unity of invention
  - V    ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI   ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand  11.05.2004	Date of completion of this report  03.01.2005
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Grammenoudi, S  Telephone No. +49 89 2399-8324  

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

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**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-91 as originally filed

**Claims, Numbers**

1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

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**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-13

because:

☒ the said international application, or the said claims Nos. 11-13 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 7,18 are so unclear that no meaningful opinion could be formed (*specify*):

**see separate sheet**

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	8-17
	No: Claims	1-6
Inventive step (IS)	Yes: Claims	
	No: Claims	1-17
Industrial applicability (IA)	Yes: Claims	1-10,14-17
	No: Claims	11-13

2. Citations and explanations

**see separate sheet**

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D1= 220th National Meeting of the American Chemical Society, Washington DC, USA, 20-24 August, 2000  
D2= WO-A-01/19814  
D3= EP-A-0 470 794  
D4= DE-A-4 407 488  
D5= Synlett, no. 8, 1999, pages 1319-1321  
D6= Australian Journal of Chemistry 53(6), 2000, pages 487-506  
D7= Helvetica Chimica Acta, 81(4), 1998, pages 676-687  
D8= Journal of the American Chemical Society, vol. 81, 1959, pages 487-490  
D9= Journal of Organic Chemistry, vol. 27, 1962, pages 1578-1581  
D10=Tetrahedron Letters, vol. 34, no. 44, 1993, pages 6993-6996  
D11=Tetrahedron Letters, vol. 34, no. 44, 1993, pages 6989-6992  
D12=Tetrahedron Letters, vol. 40, no. 17, 1999, pages 3475-3478  
D13=Römppps Chemie-Lexikon, 10. Auflage, 1996, 1997

**SECTION III**

1. For the assessment of present claims 11-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
2. Claims 7 and 18 contain references to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

**SECTION V**

1. The present application relates to phenyl derivatives, to processes for their preparation, to pharmaceutical compositions comprising them and to their use in medicine.
2. Documents D3-D12 disclose compounds which are prejudicial to the novelty of

present claims 1-6 (see D3, Example 3, compounds B, D and E; D4, page 18, compound 2E and page 22, compound 2K; D5, Schemes 1 and 2, Table 3, compounds 1a, 1b, 2a, 2b, 3a, 3b and 4; D6, Schemes 3-5, compounds 25, 26, 35, 43-45 and 47-50; D7, scheme 1, structure 4, page 680, ligands 4aa, 4ab, 4ad, 4ae, 4af and 4bb; D8, page 488, compound VII; D9, page 1579, compounds VII and VIIa; D10, page 6994, compound 6; D11, page 6989, structure 3, Table 1, entries 1-10; D12, page 3475, compounds 4 and 5). Accordingly, the subject-matter of present claims 1-6 does not meet the requirements of Art. 33(2) PCT.

3. As stated in the description on page 2, lines 5-10, the terphenyl compound 2-benzyloxy[1,1';2',1'']terphenyl-4'''-carboxylic acid is known from the art to be a ligand for the human EP<sub>1</sub> prostanoid receptor. The common concept linking together the compounds of present claim 1 is therefore not novel in view of this disclosure. Hence, claim 1 does not meet the requirements of Rule 13.1 PCT. In order for a claim using a Markush (generic) formula to be regarded as uniform, the claimed compounds should have in common a structural moiety which is distinctive in view of the prior art. This can be achieved by limiting one of the present variables to a single value not occurring in D1.
4. The problem to be solved by the present application in view of D1 is to provide other compounds binding to the EP<sub>1</sub> receptor.

This technical problem can only be regarded as having been solved if, in deciding the issue under Article 33(3) PCT, it would be credible that all phenyl derivatives claimed exhibit this activity.

It is accepted as common general knowledge that the properties of chemical compounds largely depend on their chemical structure and that even small structural differences may cause major differences in biological activity. The term "optionally substituted" used in claims 1, 4 and 5 means that the moieties concerned may be substituted by absolutely anything. Taking into account this extremely broad definition of claims 1-6, it is inherently quite unlikely that any single compound within their scope is capable of solving the problem posed. Moreover, there is no information in the description which would enable the skilled person to prepare such derivatives.

Accordingly, the subject-matter of claims 1-6 do not satisfy the requirements of Articles 33(3) and 5 PCT.

5. As far as they are novel, claims 1-6 and 8-16 do not appear to involve an inventive step in view of the teaching according to D1 and D2 (cf. D2, claim 1, page 59, lines 2-5 and page 60, line 2). The process of claim 17 is based on methods known to those skilled in the art (cf. D2, pages 28-32, Schemes 1-3) and can therefore be acknowledged only with an allowable compound claim. Thus, the subject-matter of claims 1-6 and 8-17 do not fulfil the requirements of Article 33(3) PCT.
6. The clarity of claims and their consistency with the description is of the utmost importance for the purposes of formulating an opinion on the questions whether the claimed invention appears to be novel and to involve an inventive step in view of their function in defining the matter for which protection is sought. As set out in PCT Guidelines III-4.2., the terms used in a claim are to be interpreted as having the meaning and scope which they normally have in the relevant art. Furthermore, the meaning of such terms must be clear from the wording of the claim alone.
- 6.1. The definition of the terms "alkyl", "alkoxy", "heterocyclyl", "bicyclic heterocyclyl", "aryl" and "heteroaryl" on pages 11 and 12 extends beyond the commonly accepted meaning of these terms. Thus, the terms "alkyl" and "alkoxy" do not normally include cyclic residues such as cyclopentyl or cyclopentyloxy (cf. D13, page 116). Likewise, the terms "heterocyclyl", "bicyclic heterocyclyl", "aryl" and "heteroaryl" do not embrace substituted heterocyclic, aryl or heteroaryl moieties and the expression "hetero" includes not merely oxygen, nitrogen and sulphur but also other heteroatoms (cf. D13, pages 268 and 1739). This inconsistency between claim 1 and the description (cf. page 11, line 38 - page 12, line 44) renders the scope of the claim unclear (Article 6 PCT).
- 2.2. Claims 1, 4, 7, 8 and 18 include not only compounds characterized by their chemical formulae but also "*derivatives thereof*" or "*pharmaceutically acceptable derivatives thereof*". Such definitions, however, render the scope of the claims unclear (Art. 6 PCT) since it is not possible to determine with absolute certainty whether a particular compound falls within their scope as compared to those which do not. In order to establish clarity, the above terms should have been replaced by the more precise formulation "pharmaceutically acceptable salt, ester, salt of such ester or solvate thereof" (cf. page 35, lines 35-36).
- 6.3. Claims 4 and 7 comprise all the features of claim 1 and are therefore not appropriately formulated as claims dependent on the latter (Rule 6.4 PCT).

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- 6.4. The denomination of the compound given on page 9, line 29 is obviously incomplete (Art. 6 PCT).
- 6.5. The phrases "and the like" (cf. page 11) and "or the like" (cf. page 27) render the scope of the application unclear (Art. 6 PCT).
- 6.6. The statement on page 30, lines 35-38 contradicts the requirements of Rules 5.1(a)(iii) and 9.1(iv) PCT.